

Evaluation of Nitazoxanide for the Treatment of Disseminated Cystic Echinococcosis: Report of Five Cases and Literature Review

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Abstract. We aimed to evaluate the effectiveness of nitazoxanide in disseminated cystic echinococcosis (DCE) that failed to respond to surgical and antiparasitic therapy. We report on seven patients (five of them with bony involvement): two cases from the literature and five patients who were included in a compassionate trial of nitazoxanide therapy in our hospital. Median follow-up time until nitazoxanide therapy was 12 years and all patients had received prior medical treatment and extensive surgery. Nitazoxanide (500 mg/12 h) in combination with albendazole, with/without praziquantel, was administered for 3–24 months. Three patients improved: one with muscle involvement (clinico-radiological response), one with lung involvement (radiological response), and another with soft tissue and bony involvement (clinico-radiological response of soft tissue cysts). There was one discontinuation after 15 days of starting therapy. Nitazoxanide combination therapy could have a role in the treatment of DCE when there is no bony involvement. Long-term safety profile seems to be favorable.

INTRODUCTION

Cystic echinococcosis is a zoonotic infection caused by the larval stage (metacestode) of *Echinococcus granulosus*. The parasite is perpetuated in life-cycles with carnivores as the definitive hosts harboring the adult egg-producing stage in the intestine, and intermediate host animals, in which the infective metacestode stage develops after per oral infection with eggs. The most important domestic cycle is that involving dogs and sheep in which human beings are accidental hosts. *Echinococcus granulosus* has a worldwide distribution with highest prevalence in parts of Eurasia (Mediterranean region, Russian Federation, and the People's Republic of China), Africa (northern and eastern regions), Australia and South America.^{1,2}

Although hydatid cysts may be found in almost any site of the body, the liver (68–75%) and lungs (15–22%) account for almost 90–95% of cases. The infection has also been described involving other sites such as the kidneys, spleen, abdominal or pelvic cavity, muscles, skin, brain, bones, heart, and ovaries. The severity and nature of the disease may vary, depending on the localization of the cysts, their size, and their condition.^{1,2}

Current management of cystic echinococcosis relies on four treatment modalities: surgery, percutaneous treatment, medical treatment, and a “watch and wait” approach.^{3,4} Surgery is increasingly being replaced by other options in the management of uncomplicated cysts but still maintains a central role in complicated cystic lesions. Percutaneous treatment (especially PAIR: puncture, aspiration, injection, and reaspiration⁵) for abdominal cystic echinococcosis, combined with albendazole,⁶ is a good alternative to surgery in selected active and accessible cysts. Historically, medical treatment with albendazole, with or without praziquantel, has been indicated for inoperable patients with primary liver or lung disease, patients with multiple cysts in two or more organs, peritoneal cysts, and for disseminated disease. In addition, the pre-surgical use of drugs

can reduce the relapses of hydatid disease and/or facilitate the operation by reduction of intracystic pressure.^{7–9} In the last 15 years there has been an increase in the use of medical therapy as a number of studies have been published, which suggested that medical treatment could be an alternative to surgery for uncomplicated cysts.¹⁰ The “watch and wait” approach has been recommended for uncomplicated inactive cysts (CE4 and CE5), which can be managed with regular ultrasound follow-up.³

However, these different therapeutic options, alone or in combination, have not been adequately evaluated in comparative trials.³ This is especially true for medical therapy because even after 30 years of benzimidazole use, the efficacy, optimal daily dose, and treatment duration have not been clearly established.¹¹ In the particular case of disseminated cystic echinococcosis, adequate information regarding the best therapeutic options for patients is clearly lacking.¹²

Nitazoxanide is the prototype compound of the thiazolide class of drugs. It has activity against a wide variety of microorganisms affecting humans including intestinal parasites, enteric bacteria, and the hepatitis C virus.^{13–17} It was initially developed as a veterinary antihelminthic agent against intestinal cestodes and was first described in 1984 as a human cestocidal drug.¹⁸ Additionally, there is *in vitro* and *in vivo* evidence that supports the efficacy of nitazoxanide against metacestodes of *E. granulosus*^{19,20} and *Echinococcus multilocularis*.^{21–23} Our aim was to describe the clinical effectiveness and tolerability of nitazoxanide, combined with albendazole, with or without praziquantel, in patients affected by disseminated chronic cystic echinococcosis based on our experience and a review of the literature.

METHODS

The study was carried out at the Tropical Medicine and Clinical Parasitology Unit of the Infectious Diseases Department of the Ramón y Cajal Hospital in Madrid, Spain. This Unit is a referral center for complicated cases of cystic echinococcosis. Patients have been assessed regarding medical and/or surgical management and followed-up at the unit since 1989. Nitazoxanide was administered under compassionate

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use. Every subject signed an informed consent and the drug was dispensed after approval by the hospital's medical director and the Spanish Ministry of Health.

Before nitazoxanide administration, blood count, serum biochemistry, and radiology (either magnetic resonance imaging or computed tomography) were performed for all patients. Blood tests were repeated after 4 weeks and every 8 weeks thereafter. To evaluate the response to nitazoxanide, imaging was performed at least once after 1 year of starting therapy.

Radiological response was considered when there was either an objective reduction in the extent of affected tissue involvement, a decrease in the number of lesions, or both. The radiologist was unaware of the patient's treatment history. Clinical response was defined as an improvement in the patient's clinical condition compared with the year before nitazoxanide treatment, in terms of either a decrease in the number of hospital admissions, bacterial complications (respiratory infections, skin and soft tissue infections, osteomyelitis), episodes of haemoptysis, or analgesic drug requirements.

We performed an electronic search, with no language restrictions, in MEDLINE and EMBASE to identify additional cases reported in the literature. Keywords used were "Nitazoxanide" and "Cystic echinococcosis," "*Echinococcus granulosus*" or "Hydatid disease."

CASE REPORTS

We report data on seven cases: two from the literature^{24,25} and five from our hospital (Table 1). Median patient age was 45 years (range 27–68 years) with a male to female ratio of 2.5:1. In five out of seven cases there was bony involvement (vertebral involvement). Additionally paraspinal, intrapelvic, and surrounding tissue extension was common. In one subject (case 4), cystic hydatid disease affected the liver, with vascular invasion into the inferior vena cava, right atrium, and pulmonary vasculature bilaterally. The other case without bony involvement (case 7) was a female patient with extensive involvement of the muscles of the left thigh. All patients had a chronic (sometimes progressive) course over a median period of 12 years until nitazoxanide therapy (range 3–39 years). Patients were treated during that time mainly with albendazole (400 mg twice a day continuous therapy or in 4-week on 2-week off cycles) with or without cimetidine (400 mg or 200 mg twice a day) or praziquantel (600 mg three times a day). Multiple surgical interventions were performed for all patients but one during the course of the disease.

Nitazoxanide treatment was prescribed at a dose of 500 mg twice a day in combination with albendazole, with or without praziquantel. In one case (case 2), nitazoxanide medical therapy was associated with surgical treatment. One subject was treated for 15 days only because of gastrointestinal intolerance (case 6). For the other six patients, length of therapy ranged from 3 months (two patients, with an additional month in case 1²⁵), to 24 months. In two out of those six patients (cases 3 and 5), nitazoxanide was discontinued after 18 and 24 months of therapy, respectively, given that neither clinical nor radiological responses were clearly obtained. Cases 4 and 7 were still on nitazoxanide therapy at the end of the study period.

Responses to treatment were disparate. In cases 2, 3, and 6 there was worsening of the disease with dissemination of cysts and appearance of new lesions. For cases 1 and 5 response

was discordant: although bony lesions did not change, there was a significant improvement in soft tissue disease in case 1, and a mild improvement in paraspinal tissue involvement in case 5. In contrast, cases 4 (Figure 1) and 7 (Figure 2) showed radiological improvement, particularly in case 7 where a clear clinical response was evident as well. Before nitazoxanide treatment, one patient (case 7) had two active draining fistulae in the thigh, limiting pain in the limb, needed a crutch to walk, and had suffered from several episodes of bacterial cellulitis; one of which required hospital admission. PAIR was performed twice before starting nitazoxanide but given the number, extension, and trabeculation of cysts, the procedures were not effective. Extensive excisional surgery was not performed because adequate healing was not feasible, and the patient was a Jehovah's Witness, and a blood transfusion would not have been allowed if needed. After nitazoxanide treatment the number and extent of the lesions decreased, fistulae resolved, pain disappeared, and the patient no longer needed crutches.

The incidence of adverse events could be evaluated in six subjects: one patient (case 6) interrupted nitazoxanide because of a morbilliform pruritic rash 15 days after starting therapy; and another patient (case 4) stopped nitazoxanide after 15 days because of severe watery diarrhea and weight loss, but treatment could be reintroduced at half the dose after 20 months. The other four patients did not have side effects apart from moderate constipation (case 5) that resolved after treatment discontinuation.

DISCUSSION

Disseminated cystic echinococcosis is a devastating and complex disease in which medical and surgical approaches are not standardized.¹² Furthermore, treatment decisions based on WHO cyst classification cannot usually be applied.²⁶ The low frequency of this form of the disease (less than 10% of all cystic echinococcosis cases), the decreasing incidence in former prevalent areas (like the Mediterranean basin), the different clinical manifestations that may preclude uniform approaches, and the lack of randomized clinical trials, are all factors contributing to this uncertainty. Surgery, when feasible, and long-term chemotherapy are currently the treatments of choice for these cases, although outcomes may vary.^{3,12,27–30}

Benzimidazoles (mebendazole 40–50 mg/kg/day and albendazole 10–15 mg/kg/day) are the drugs of choice for the medical treatment of cystic hydatid disease. Serum drug levels may vary widely in individual patients and thus correlation between oral doses and drug efficacy is inconsistent. Their administration with a fatty meal improves intestinal absorption.³¹ Albendazole has largely replaced mebendazole because of its greater intestinal absorption, more convenient dosing, and higher efficacy.³² Monthly cyclic treatment with 14-day intervals was originally recommended, but continuous therapy for 3 to 6 months or longer has demonstrated equal or even improved efficacy without an increase in adverse events.³³ Common adverse reactions associated with albendazole treatment are elevation of transaminases (14.7%), hair loss (2.8%), headache (2.1%), reversible leucopenia (1.2%), and bone marrow toxicity (0.1%) that may lead to treatment interruption in less than 4% of patients.^{1,31} The efficacy of albendazole depends on a variety of factors,^{3,11,31} including cyst size (those

TABLE 1
Characteristics and outcome of the seven patients treated with nitazoxanide*

Report	Age (years) sex	Hydatid disease extension before NTZ therapy	Medical and surgical treatment before NTZ therapy	Medical and surgical treatment associated with NTZ therapy	NTZ adverse events	Outcome
Case 1 Winning and others, 2009 ²⁵	68/F	Left femur, hip, pelvis, and surrounding soft tissues. Pain and spontaneous discharge from the left hip.	1975–88: intermittent MEB courses. 1988–04: ALB 400 mg bid 4-weeks on 2-weeks off. 2004–06: PZQ 600 mg tid is added on the first day of each ALB cycle.	2006: NTZ 500 mg bid + ALB 400 mg bid 3 months, then ALB 400 mg bid An additional 1-month course of NTZ was dispensed (time not specified)	Treatment was well tolerated	Significant regression of the soft tissue cysts in abdominal wall and lateral to the left iliac wing, with stable bony disease. Decrease in hip pain and swelling. Patient was admitted after second NTZ cycle caused by septic shock (suspected secondary bacterial infection of the hip sinus), and died because of a cerebral hemorrhage. Progressive and disseminated disease: spinal (Th12), sacral (S1–S2) and paraspinal extension; left sacroiliac joint invasion, pelvic destruction and dissemination toward the skin and inside the spinal canal.
Case 2 Schipper and others, 2009 ²⁴	39/M	Lumbar spine L3–L5	1993–05: ALB 400 mg bid + Cimetidine 400 mg bid 1993–05 several surgical interventions in lumbar spine	2005: NTZ 500 mg bid + ALB 800 mg bid 3 months preceding spondylosis of L3–L5 and laminectomy of L4. After surgery ALB 800 mg bid ± cimetidine 400 mg bid was started (3 years). 2008: Percutaneous treatment (PAIR)	NR	
Current study case 3	37/M	Right lung hydatidosis, extensive spinal (Th3–Th7) and paraspinal involvement, cord compression, bronchopleural fistulae, and bacterial osteomyelitis D3–D4. Episodic respiratory bacterial infections secondary to cyst superinfection	1997–08: ALB 400 mg bid + PZQ 600 mg tid 122 months ± cimetidine 200 mg bid 1997–08: several spinal surgi- cal interventions, osteo- synthesis and paraspinal abscess drainage	April 2008: NTZ 500 mg bid + ALB 400 mg bid + PZQ 600 mg tid 18 months, then ALB 400 mg bid + PZQ 600 mg tid	No clinical or laboratory adverse events.	No clinical or radiological improvement. MRI (month +17 after starting NTZ Tx) and CT (month +19) revealed new lesions inside the thoracic spinal canal.
Case 4	27/M	Liver, cardiac, endovascular (vena cava), and extensive bilateral lung disease	2003–05 and 2007–08: ALB 400 mg bid 39 months + PZQ 600 mg tid 27 months 2003: partial hepatectomy and resection of cardiac and inferior vena cava cysts. 2007 and 2008: Bronchial artery embolizations (caused by hemoptysis)	April 2008: NTZ 500 mg bid + ALB 400 mg bid + PZQ 600 mg tid 15 days, then ALB 400 mg bid + PZQ 600 mg tid January 2010: NTZ 500 mg qd + ALB 400 mg bid + PZQ 600 mg tid 18 weeks	Severe watery diarrhea and weight loss. Good tolerance when reintroduced at half dose	Radiological improvement. CT (month +12 after first cycle, month +5 and +6 after second cycle of NTZ) showed improvement in sev- eral lesions and healing of three cysts.
Case 5	45/M	Lung and spinal (Th7–Th11) disease with cord compression. Paraspinal abscess. Hemoptysis and bronchopleural fistulae. Episodic respiratory bacterial infections secondary to cyst superinfection	1993–2008: ALB 400 mg bid + PZQ 600 mg tid 97 months 1993–2005: surgical spinal cord decompression and paraspinal abscess drain- age. 2007: bronchial artery embolization	April 2008: NTZ 500 mg bid + ALB 400 mg bid + PZQ 600 mg tid 24 months, ALB 400 mg bid + PZQ 600 mg tid	Constipation (resolved after NTZ interruption)	No clinical improvement. CT (month +12 and +25 after start- ing NTZ Tx) showed no improve- ment in bony involvement but mild improvement in paraspinal soft tis- sue disease.

(Continued)

TABLE 1
Continued

Report	Age (years) sex	Hydatid disease extension before NTZ therapy	Medical and surgical treatment before NTZ therapy	Medical and surgical treatment associated with NTZ therapy	NTZ adverse events	Outcome
Case 6	52/M	Intra-abdominal, pelvic, spinal (Th11-L5), sacral, iliac bone, and gluteus muscle involvement. Inguinal and gluteal fistulae. Spinal cord compression with transverse myelopathy and paraplegia	2005-2008: ALB 400 mg bid 4-weeks on 2-weeks off 24 months + PZQ 600 mg tid 31 months 1972-2005: Right nephrectomy, several spinal interventions and intra-abdominal abscess drainage	April 2008: NTZ 500 mg bid + ALB 400 mg bid + PZQ 600 mg tid 15 days, then ALB 400 mg bid + PZQ 600 mg tid 24 months	Morbiliform and pruritic rash that led to discontinuation of NTZ.	No clinical improvement, progression of disease (number of lesions and extension). CT (month +18 after starting NTZ Tx) revealed new intrapelvic cyst and growth of previous cysts.
Case 7	68/F	Extensive muscular involvement of left thigh without bone involvement. Several episodes of bacterial cellulitis secondary to fistulae/drainage of infections	2007-2008: ALB 400 mg bid 14 months 1969-2007: several surgical interventions for drainage, excision and marsupialization of cysts. 2007: PAIR	April 2008: NTZ 500 mg bid + ALB 400 mg bid 24 months	No clinical or laboratory adverse events.	Clinical and radiological improvement. CT and MRI (month +12 and +23 respectively) showed marked reduction in number and size of cysts.

* ALB = albendazole; BID = twice a day; CT = computed tomography; F = female; M = male; MEB = mebendazole; NR = not reported; NTZ = nitazoxanide; PAIR = puncture, aspiration, injection and reaspiration; PZQ = praziquantel; MRI = magnetic resonance; QD = once a day; TID = three times a day; Tx = treatment.

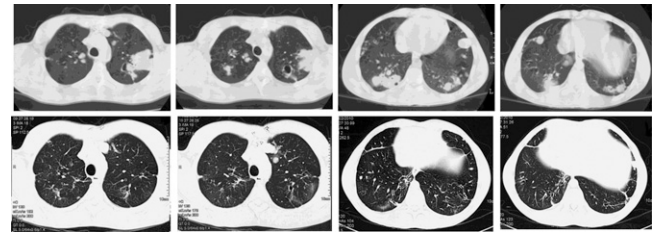


FIGURE 1. Computed tomography scan of patient number 4 before (upper row) and after (lower row) 20 weeks of Nitazoxanide therapy, between April 2008 (15 days of therapy at 400 mg twice daily) and April 2010 (18 weeks of therapy at 400 mg once daily since January 2010).

with < 5–6 cm in the liver and lung respond favorably), cyst stage (better response for CE1 and CE3a), and location (bone cysts are less sensitive). With respect to liver and lung cystic echinococcosis, it has been estimated that 2 years after treatment initiation 40% of cysts are still active or become active again.¹¹

Praziquantel has shown to have antiparasitic activity and has been recommended as combination therapy with albendazole. The synergistic effect of both drugs may be due in part to the increase in the plasma levels of albendazole metabolites (sulphoxide) when they are given simultaneously.³⁴ Combined therapy seems to reduce the length of treatment,³⁵ and it is particularly recommended pre-surgery and in bony or disseminated hydatidosis.⁹ However, there is a relative lack of information regarding dose, frequency of dosing, and length of combination therapy to establish evidence-based recommendations.

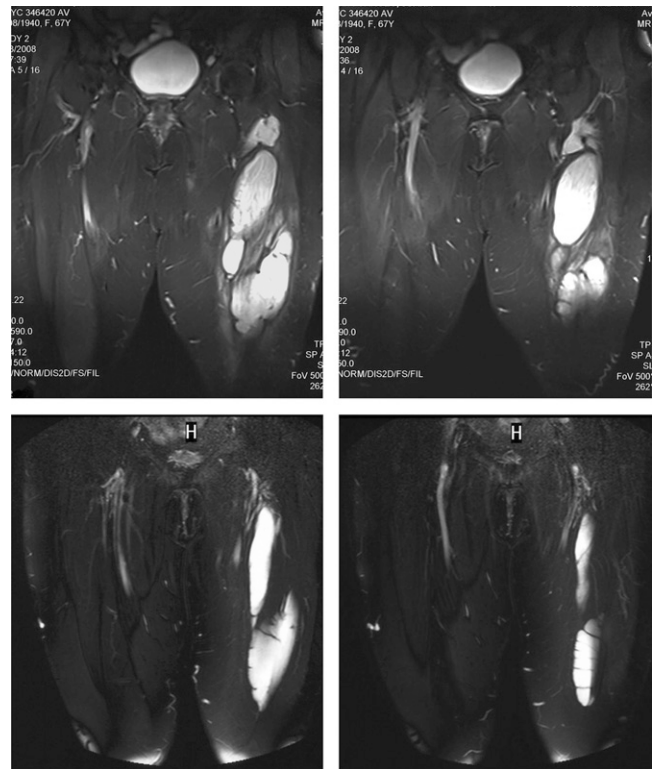


FIGURE 2. Magnetic resonance imaging scan of patient number 7 before (upper row) and after (lower row) 24 months of nitazoxanide therapy at 400 mg dose twice daily, between April 2008 and April 2010.

In the seven patients presented in this report, cystic echinococcosis progressed or continued its protracted course despite extensive surgical and medical treatment during a time period ranging from 3 to 39 years (median 12 years). Thus, the concomitant use of nitazoxanide in a combination regimen was considered. Nitazoxanide is a thiazolide with structural resemblances to benzimidazoles that was licensed in the United States for the treatment of *Cryptosporidium parvum* and *Giardia lamblia*.^{36,37} Its mode of action is unknown though it has been postulated that nitazoxanide may interfere with the enzyme-dependent anaerobic energy metabolism of parasites.¹⁷ This drug has shown to be active *in vitro* and *in vivo* against *E. multilocularis*^{21–23} and *E. granulosus*.^{19,20}

Nitazoxanide is highly effective against *E. multilocularis* larvae. Times until larval vesicles showed first signs of degeneration and until disintegration of all vesicles, were significantly shorter for nitazoxanide compared with albendazole when high doses of 10 µg/mL were studied, thus showing the parasitostatic potential of nitazoxanide when given as a single-drug treatment *in vitro*.²³ Nitazoxanide has also demonstrated parasitocidal activity on metacestodes, and this effect has been confirmed in bioassays in mice.²² Nevertheless, more promising results come from the combined treatment of nitazoxanide and albendazole that has shown parasitocidal activity *in vitro*²³ and *in vivo*.²¹ In a murine experiment, the combination of nitazoxanide and albendazole against *E. multilocularis* metacestodes most effectively reduced the parasitic mass in a model of secondary infection. Moreover, the administration of albendazole and nitazoxanide in combination resulted in a 2- to 4-fold increase of albendazole sulfoxide serum levels compared with the application of albendazole alone.²¹ The efficacy of nitazoxanide has also been demonstrated *in vitro* against *E. granulosus*, where it exhibits protoscolicidal activity and effects on the metacestode stage.¹⁹ However, it did not show a clear synergistic effect in combination with oxfendazole for the treatment of naturally infected sheep.²⁰

In this series, all patients but one was treated with nitazoxanide combination therapy for prolonged periods of time (3 to 24 months). In all but one the drug was administered at standard doses (500 mg twice a day), and one patient additionally underwent surgery. Only three patients appeared to respond to therapy: cases 4 and 7 that presented lung and muscle involvement, respectively, without bony dissemination, and case 1 who responded partially (improvement in soft tissue but not the bony lesions). Bone involvement, especially of the spine and pelvis, is very difficult to treat and has a poor prognosis.^{28,30} In addition, albendazole penetration in bone is probably low. Thus, response to therapy in these three patients was possibly not only secondary to antiparasitic drugs, but caused by a combination of drug therapy and specific disease localization. We also do not believe this response could be attributed to albendazole, with or without praziquantel, therapy alone during a prolonged follow-up period (follow-up time bias), given the stability of lesions for a long period of time before nitazoxanide therapy.

One of the areas of uncertainty in the long-term treatment of cystic echinococcosis with nitazoxanide is safety, mainly when it is combined with albendazole and praziquantel. This drug has shown a very favorable toxicity profile in short-term therapy.^{37,38} Most common adverse events reported in studies of treatment of either *G. lamblia* or *C. parvum* infections, regardless of causality assessment, were abdominal pain

(6.6%), diarrhea (4.2%), headache (3.1%), and nausea (3.0%). Less than 1% of patients discontinued therapy because of an adverse event. Its long-term safety profile has been evaluated in patients treated for hepatitis C (24 to 48 weeks),^{16,39} the rate of clinical and laboratory adverse events being equivalent in nitazoxanide and placebo groups. In this series, tolerance over a period of 3 to 24 months was good taking into account that all patients were also receiving albendazole, and four of them were also on treatment with praziquantel. In one case treatment had to be interrupted because of an adverse reaction (morbilliform pruritic rash). One patient suffered from mild constipation that disappeared when the drug was interrupted because of nitazoxanide ineffectiveness, and another patient (taking albendazole and praziquantel) developed severe diarrhea but could tolerate the drug at half the usual dose. Nitazoxanide seems to be well tolerated with only mild toxicity, even in patients with complex and prolonged medical therapy.

In summary, nitazoxanide combination therapy seems to be active for disseminated cystic echinococcosis affecting soft tissues, muscles, or viscera, and apparently it has no role in chronic and extensive bony lesions. The long-term safety profile is good and intolerance, if it occurs, is an early phenomenon. Clinical trials with standardized diagnostic, and therapeutic procedures, are warranted to determine the potential role of nitazoxanide as monotherapy or in combination with albendazole in the treatment of this parasitosis.

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